Precursors of cognitive impairments in psychotic disorders: a population-based study

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Precursors of cognitive impairments in psychotic disorders: a population-based study

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ABSTRACT

Cognitive deficits have been found to be more prevalent in psychotic than in other disorders. Longitudinal research has shown that these deficits were generally already existent before onset of illness and are therefore not necessarily attributable to neurodegenerative processes. This study investigated whether both low IQ and markers of premorbid cognitive dysfunction independently contribute to an increased risk for psychoses. In a cross-sectional study about 50.000 young Swiss males completed a survey of intellectual problems in childhood/adolescence and other vulnerability factors during military call-up in 2005/2006. Subsequently, military IQ assessments were carried out on the entire sample. Diagnostic assessments were conducted according to ICD-10. Low, especially performance IQ was highly associated with an increased risk for psychotic disorders after adjusting for preexisting cognitive deficits and covariates; while in other disorders this association was less marked. Furthermore, preexisting intellectual problems emerged as important risk factors for psychoses. Our results confirm the importance of low IQ as characteristic of psychoses. Although premorbid intellectual deficits are common in people who go on to develop psychosis, neurodegenerative disease processes may also precipitate further declines in fluid cognitive functions. Assessment of cognitive functioning should be taken into account in early detection of psychoses.

Key words: *Mental disorders, psychosis, cognitive deficits, verbal and performance IQ, markers of premorbid cognitive impairments*

1. Introduction

There is evidence that several psychiatric disorders are linked to subtle or in some cases serious cognitive deficits (Quraishi and Frangou, 2002). Indeed for in schizophrenia and other psychoses cognitive deficits are considered to be a core feature of the disease and are therefore well investigated (for an overview see Matheson et al., 2011). However, more recent prospective studies suggested cognitive impairments might have their origins several years prior to the psychotic break and are therefore not attributable to onset and course of the illness (Rund, 1998; Amminger et al., 2000; van Winkel et al., 2006; Kremen et al., 2010; Mechelli et al., 2011). A meta-analysis of longitudinal population-based studies provided strong evidence for pre-morbid cognitive deficits in future cases of psychosis (Khandaker et al., 2011). According to the neurodevelopmental hypothesis of schizophrenia abnormal brain development is a solid marker for neural processes, which predispose for psychotic symptoms and therefore increases the risk for psychosis (Murray and Lewis, 1987; Weinberger, 1987). Such processes are assumed to have their onset very early in life, probably pre-birth, so that subtle cognitive and attention abnormalities in most individuals who subsequently develop schizophrenia are already present (and detectable) during childhood and adolescence (Murray and Lewis, 1987; Silverstein et al., 2002; Niemi et al., 2003; Harvey, 2009; Kremen et al., 2010). Furthermore, family studies showed that cognitive deficits are likely even in non-affected relatives of psychotic individuals suggesting that a genetic predisposition might contribute to both later intellectual performance and increased risk of developing schizophrenia (Rabinowitz et al., 2000; Reichenberg et al., 2000; Cannon et al., 2002; McDonald and Murphy, 2003; Ross et al., 2008; Jundong et al., 2011). Studies on monozygotic twins discordant for schizophrenia found cognitive impairments in both twins, however, the twin with psychosis generally obtained lower scores than the

unaffected twin (Goldberg et al., 1990). An additional subtle cognitive decline during the late prodrome is likely - i.e. prior to the first episode when early disease processes may precipitate neurodegenerative changes (Harvey, 2009; Aoyama et al. 2011). It should, however, be stated that such cognitive decline does not necessarily reflect a functional loss, rather it is linked to an inability to acquire new information and skills (Bedwell et al., 1999). Since these changes have generally already occurred by the time a prodrome is detected it remains unclear when exactly they occurred (Harvey, 2009). However, it seems to suggest that cognitive deficits, which are related to psychotic disorders, are not necessarily consequences of illness but rather potential markers of increased vulnerability for psychosis.

The main aim of the study was to examine neuropsychological differences between diagnostic groups and healthy controls according to the classification manual of the World Health Organization (WHO), the International Classification of Diseases – 10th edition (ICD-10; WHO, 2004). Of particular interest in this study was the exploration of whether IQ deficits are characteristic features of psychotic disorders. We further evaluated whether cognitive deficits, which were present earlier in life were associated with an increased risk for psychoses. We identified intellectual problems in childhood/adolescence as potential markers for premorbid cognitive deficits. For this purpose we linked survey data of military conscription, cognitive testing and diagnostic assessments in a cohort of Swiss conscripts of the years 2005 and 2006. This design enabled us to address the questions of whether intellectual deficits were present before the onset of a disorder or alternatively whether they might be attributable to neurodevelopmental changes during illness.

2. Methods

2.1. Sample and procedure

Swiss males between 18 and 22 years are obliged to undergo military conscription regardless of whether they will eventually serve in the Armed Forces. The examination of physical and mental fitness includes a psychiatric screening questionnaire (Mueller et al., 2009) and IQ testing of cognitive ability (Huber, 1999). Conscripts showing any abnormal behavior during testing or reporting any psychological problems during screening surveys were referred to a clinical military psychologist or psychiatrist for further clinical diagnostic examination.

The present study uses data collected on Swiss Armed Forces conscripts in 2005 and 2006. Of the 51,498 males who completed the psychiatric screening questionnaire, 346 were excluded from analyses due to missing IQ data. Those conscripts who received a diagnosis of organic mental disorders (Code F00-F09; N=17) or mental retardation (Code F70-F79; N=514) were also excluded since their cognitive state will be principally determined by these conditions. In order to avoid biased results due to individuals who may be in the prodromal stage of psychiatric illness, those conscripts that received a psychiatric diagnosis during their following basic military training (BMT) were also excluded (N=1,076; 2.13% whereof N=14; 0.03% received any F2-diagnosis). The average time between conscription and diagnosis for those individuals was 392.0 days (SD=180.6). Finally, 49,545 subjects (mean age=19.72 years, SD=1.02) were left in the dataset and used for the purpose of analysis.

This study was a collaboration between the Medical Department of the Swiss Armed Forces and the Centre for Disaster and Military Psychiatry at the University of Zurich. It was further cleared by the Zurich State Ethical Committee (KEK) to fulfill all legal and

data privacy protection requirements. All screening and test sessions were introduced and supervised by military test psychologists.

2.2. Diagnostic assessment

All clinical diagnoses were given by professional clinicians according to ICD-10. Following screening, 8,444 conscripts (17.04%) were diagnosed with a psychiatric disorder during conscription: 3,997 of these (8.07%) received a diagnosis of alcohol and substance use disorders (F10-19), 61 (0.12%) schizophrenia and related psychoses (F20-29; assessed by the subcategories: 1.) schizophrenia, schizotypal and delusional disorders (N=29), 2.) acute and transient psychotic disorders (N=9), 3.) schizoaffective disorders (N=11), and 4.) Other or unspecified non-organic psychotic disorders (N=12)), 753 (1.52%) mood disorders (F30-39), 3,134 (6.33%) neurotic and anxiety disorders (F40-49), 1,095 (2.21%) psychosomatic disorders (F50-59), 1,328 (2.68%) personality disorders (F60-69), 126 (0.25%) developmental disorders (F80-89), and 1,196 (2.41%) behavioral and emotional disorders with onset in childhood or adolescence (F90-99).

Due to psychiatric comorbidities most subjects received more than one psychiatric diagnosis. For the purpose of this study each subject was assigned to only one diagnostic category based on clinical severity. We used the following hierarchic strategy: 1.) Psychotic disorders (i.e., schizophrenia and related psychoses - F20-29), 2.) mood [affective] disorders (F30-39), 3.) Neurotic and anxiety disorders (F40-49), 4.) Personality disorders (F60-69), and 5.) Other psychiatric disorders (remaining ICD-10 F-codes except F0x and F7x [see sample description]). Thus, if a conscript received at least one ICD-10 diagnosis of psychotic disorders he was assigned to the diagnostic category “psychotic disorders”. If he was not diagnosed with any psychotic disorder but

with any mood disorder he was assigned to the category of "mood disorders". Further, if he was not diagnosed with any mood disorder but with any neurotic or anxiety disorder he was assigned to the category of "neurotic and anxiety disorders" and so forth for "personality disorders" and finally all remaining F-diagnoses were included in the last category "other psychiatric disorders". Proportions of each category as used in the present study are shown in Table 1.

2.3. IQ assessment

Full scale (FSIQ), verbal (VIQ) and performance IQ (PIQ) were obtained for each subject from the Intelligence Test 95 (T95; Foppa et al., 1997; Huber, 1999) which was developed according to the Berlin Model of Intelligence Structure (BIS; Jäger, 1982). Two time-limited IQ subtests assessed verbal (synonym and vocabulary abilities) and performance tasks (recognition abilities) with 30 items each. Both subscales have been thoroughly validated (Huber, 1999); revealing that the VIQ correlated highly with the verbal subscale (r=0.68) of the Wilde Intelligence Test (WIT; Althoff and Jäger, 1983) and the PIQ was highly correlated with the Form Board Test (r=0.52) of the Kit of Factor-Referenced Cognitive Test (KIT; Ekstrom et al., 1976). FSIQ range from 0 to 60 and subtest scores range from 0 to 30. The test scores has been language of test standardized (German, French, Italian), and converted to IQ-type scale scores (mean=100; SD=15).

2.4. Preexistent cognitive problems

Assessment of earlier intellectual abnormalities was gathered in order to provide information on past cognitive functioning, i.e. prior to clinical assessment. Presence of intellectual abnormalities in childhood and adolescence was assessed by asking the following questions: a.) Did you complete compulsory school?, b.) Did you ever have to repeat a class?, c.) Did you ever have to have a psychological assessment due to learning difficulties?, or d.) Was a diagnosis of dyslexia ever given? Every question answered with "yes" was considered as a marker for preexisting cognitive problems or deficits.

2.5. Developmental factors

In order to control for other vulnerability factors which predispose for mental health problems subjects were asked whether any member of their nuclear family was ever diagnosed with a psychiatric disorder. A list with psychiatric disorders (schizophrenia or other psychoses, depression, anxiety disorders, obsessive-compulsive disorders, and other psychiatric disorders) was presented which was to be answered with "yes", "no", or "I don't know" (coded as missing response for our analyses).

Moreover, obstetric problems have frequently been found to be associated with increased risk of later psychopathology (Gunnell et al., 2002) therefore subjects were asked whether any complications occurred during their own birth ("yes" or "no"). Don't know-answers were also coded as missing for the purpose of our analyses.

2.6. Statistical analysis

First of all, those initially undiagnosed individuals who developed any psychiatric disorder during BMT (study dropouts) were compared to the study subsample without

any psychiatric diagnosis. For the study sample, raw IQ mean scores were calculated for each diagnostic category and displayed as graphs (Figure 1). Bivariate associations between categorical variables were analyzed by cross tabulations and Chi-Square statistics. Relative risks for any diagnostic category with regard to the factors under consideration were estimated via multinomial logistic regression models with healthy controls as reference category. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Unadjusted models provide crude ORs for the relation between diagnostic category and IQ levels (full and subscales), markers for preexistent intellectual problems (repeated class, dyslexia, not finished compulsory school and psychological treatment due to learning difficulties) and developmental factors (psychiatric disorders in family and birth complications). Adjusted models (separately for full and subscale IQ) were calculated with those variables that were significantly related in unadjusted models. All analyses were performed using STATA 10.2 (StataCorp, 2007).

3. Results

3.1. Dropout analyses

To describe those who were excluded from the study sample, simple mean difference tests for IQ scores as well as Chi-square tests for categorical variables against the study subsample of healthy controls were conducted (see Table 1). Those with later psychotic disorders showed considerably lower full and subscale IQ scores (albeit not significant) than controls whereas the mean differences for other psychiatric diagnoses were smaller but significant. No differences between IQ subscales were observed for dropouts. Compared to controls dropouts reported significantly more often not having

completed compulsory school and/or had repeated a class in school. These proportions were highest for dropouts with later diagnosed psychotic disorders.

3.2. Study analyses

Initial comparisons of raw IQ scores between diagnostic categories revealed that subjects with psychotic disorders scored significantly lower than controls on PIQ and at trend level on FSIQ (see Table 1). Subjects assigned to any other diagnostic categories scored significantly lower than controls on full and subscale IQ except for those with mood disorders who scored significantly lower only on PIQ scores. These differences were highest for those with psychotic disorders.

Preexisting intellectual problems were invariably found to be higher in those with psychoses than in any other diagnosis (see Table 1). For example, 12.50% of subjects with psychosis did not finish compulsory school compared to less than 5% in other diagnostic categories and less than 2% in controls. Furthermore, more than half (55.17%) of those diagnosed with psychosis repeated a class at least once in school which is almost double the rate seen in other categories (26.81% to 38.50%). In controls the rate is less than a quarter (22.03%). About a third of those with psychosis (29.82%) were previously assessed by a psychologist or had received treatment due to learning difficulties (vs. <24% in other diagnostic categories and <8% in controls). More than 15% of those with psychosis reported being diagnosed with dyslexia, followed by mood disorders (<13%) and less than 11% in other diagnostic categories (vs. <8% in controls).

Psychiatric disorders in family show highly congruent patterns with diagnostic categories (see Table 1). One third of those conscripts diagnosed with psychosis (32.73%) reported having a family member with a psychotic disorder (vs. <18% in other

diagnostic categories and < 3% in controls). Familial depressive disorders were most often reported by those diagnosed with mood disorder (69.34%), followed by personality disorders (52.15%), psychoses (51.79%) and other diagnostic categories (<50%) and controls (17.10%). Those diagnosed with a mood disorder also reported most often having a family member with an anxiety disorder (31.84%) followed by personality disorders (27.68%), other diagnostic categories (<25%) and controls (6.42%). Obsessive-compulsive disorders were most frequently reported in those with mood (11.56%), psychotic (9.43%) and personality disorders (8.90%), followed by other diagnostic categories (<7%) and controls (1.50%). Birth complications were more frequently reported by those with mood disorders (24.61%) and psychosis (23.21%) followed by other diagnostic categories (about 21%) and controls (11.11%). For more detailed information, refer to Table 1.

- Insert Table 1 -

Table 2 shows the bivariate associations of current IQ scores with markers of earlier intellectual problems and other covariates. Results revealed significantly lower IQ scores for those with preexisting intellectual problems. Poorest IQ scores were found in those who had not finished their compulsory schooling (FSIQ < 90) and those with formerly diagnosed dyslexia (VIQ < 88). No such systematic or nonsignificant associations were found for IQ distributions across developmental factors (familial psychiatric disorders and birth complications). Particularly, slightly higher scores were found in those with familial disorders.

- Insert Table 2 -

Table 3 shows the unadjusted probabilities of the bivariate associations displayed in Table 1. FSIQ was negatively related to psychiatric disorders with the exception of mood disorders. In particular psychotic disorders were associated with a 30% decreased probability by any increase of IQ by one standard deviation (=15 IQ points) over average compared to controls. Associations of IQ and other diagnostic categories were found to be slightly weaker (see Table 3). VIQ was unassociated to psychotic and mood disorders while slightly negative associated with other diagnostic categories (ORs: 0.83 to 0.89). Low PIQ was highly associated with an increased risk for psychosis (+36% per decreasing 15 IQ points). Mood disorders were associated exclusively with PIQ (OR=0.88) while this association in other diagnostic categories was similar as to FSIQ.

Preexistent intellectual problems were consistently highly associated with psychiatric disorders compared to controls. In particular, the risk for psychosis was significantly increased by all of these factors. Accordingly, having not finished compulsory school increased the risk for psychosis by a factor of 9.6 (vs. 1.6 to 3.5 for other diagnostic categories), having repeated a class by the factor of 4.4 (vs. 1.3 to 2.2 for other diagnostic categories), psychological review due to learning difficulties by a factor of 5 (vs. 2.9 to 3.6 for other diagnostic categories), and dyslexia by a factor of 3.7 (vs. 2.3 to 3.1 for other diagnostic categories).

Furthermore, self-reported familial psychiatric disorders highly increased the probability of any clinical diagnosis. The strongest associations were psychotic disorders to familial psychotic disorders (OR=17) and mood disorders to familial

depressive disorders (OR=11). Finally, complications at birth increased the risk for any psychiatric disorder by more than twofold. For more details please refer to Table 3.

- Insert Table 3 -

Adjusted models revealed similar results to the unadjusted models (see Table 4). Associations between disorders and IQ slightly increased for psychotic and mood disorders whereas other diagnostic categories slightly decreased in their relationship or remained stable, respectively. Accordingly, FSIQ and PIQ are similarly negative-associated with psychotic disorders (ORs: 0.66/0.64) while an attenuated risk was found for other diagnostic categories in relation to full and subscale IQ (ORs: 0.78 to 0.92). Preexistent intellectual problems were independently associated with an increased risk for all diagnostic categories. In particular, the risk for psychotic disorders was significantly increased when compulsory schooling was not completed (by factor 3.1), a class was repeated or a psychological assessment due to learning difficulties was required (by factor 2.4). Furthermore, the risk for personality disorders or diagnostic category "other psychiatric disorders" was increased for those who did not complete compulsory schooling (ORs 1.9/1.7) and repeated class increased the risk for personality disorders by 50%. In addition, psychological treatment for learning difficulties was significantly associated with an increased risk for all diagnostic categories, especially for psychotic disorders and "other psychiatric disorders" (ORs: 2.4). Dyslexia was not a specific predictor for psychoses rather for mood disorders (OR=1.8) and, to a lesser extent, for neurotic and anxiety disorders and "other psychiatric disorders" (ORs: 1.3).

Diagnostic categories were strongly associated with the corresponding category of familial psychopathology in cases of psychosis (OR=5.8) and depression (OR=5.4). Other diagnoses as well as category crossovers showed much lower associations. Birth complications were associated with a greater than 50% higher probability for all diagnostic categories other than psychotic disorders where no correlation was found.

- Insert Table 4 -

4. Discussion

The objective of the present study was to examine whether and to what extent cognitive deficits are an integral part of psychotic disorders. Furthermore, we aimed to address the question of whether in such cases early signs of cognitive deficits were already present in childhood and adolescence or whether low IQ might be rather a result of a cognitive decline associated with acute phases of a psychotic illness. Analyses were adjusted for other covariates such as familial liability and birth complications.

Our findings strongly support a link between cognitive deficits and psychotic disorders with further evidence of the existence of premorbid intellectual problems in those who were later diagnosed with a psychotic disorder. In detail, IQ scores were found to be negatively associated with a psychotic diagnosis. This association, however, was primarily a result of poor PIQ. Thus, although there is a negative link between FSIQ and psychotic disorders primarily low PIQ was strongly related to psychoses whereas this was not the case for VIQ.

This finding in which subjects with psychotic illnesses perform more poorly on performance than on verbal intelligence tasks is consistent with earlier research showing that primarily fluid functions are negatively affected in psychotic individuals (Aylward et al., 1984; Ott et al., 1998; Amminger et al., 2000). This gap between deficits, however, is assumed to vary according to the stage of illness. In premorbid stages there are only small differences between specific IQ deficits whereas in a first episode and even more in chronic schizophrenia greater deficits in PIQ than that in VIQ were observed (Heinrichs and Zakzanis, 1998; Rajji et al., 2009; Khandaker et al., 2011). This view of a progressing IQ differential could be approximated by our data. Thus, while no differences were found in controls, lower PIQ than VIQ scores were assessed in "prepsychotic dropouts" up to large differences in current psychotic cases. In another but prospective conscript study, a general cognitive impairment was found to be predictive of later disorders from the schizophrenia spectrum, however, an additional risk was given by deficits in nonverbal reasoning (comparable to PIQ) (Reichenberg et al., 2006). This effect might be explained by neurodegenerative processes in specific areas of the brain during illness which involve fluid components of intelligence such as executive functions and working memory (Purcell et al., 1998; Amminger et al., 2000; Ojeda et al., 2010). While basic functions are intact those functions which enable the acquisition of new information and skills are impaired (Bedwell et al., 1999). However, it should be mentioned that not all individuals with psychotic disorders performed poorly on the given IQ tasks. Thus, low mean IQ scores in the psychotic subsample might be due to a minority effect, i.e. only a subgroup of those with psychosis have particularly low IQs (Khandaker et al., 2011). Theoretically, the results further suggest higher intelligence to be protective against psychosis. An alternative model suggests that higher intelligence may act as a buffer against the effects of separate processes that modify

(increase) the risk for psychosis (Khandaker et al., 2011) and therefore may act as protective factor (Reichenberg et al., 2006).

Moreover, our results clearly indicate, as hypothesized, that markers for preexistent cognitive impairments are most prevalent among subjects diagnosed with psychoses. Adjusted models revealed that learning difficulties in particular (repeating class, not completing school, and psychological treatment due to learning difficulties) have already been present in early life in those who were subsequently diagnosed with psychosis (Maydell et al., 2009; Goulding et al., 2010). These earlier problems directly increased the probability for subsequent psychosis by two to three times - significantly more than for any other diagnostic category. Although both earlier school problems and low IQ independently contributed to an increased risk for psychosis, their bivariate associations provide evidence for an early manifestation of any intellectual deficits. Similar effects were also found in other diagnostic categories, they were, however, generally less specific and less severe than in psychotic disorders. This finding supports the link between premorbid cognitive deficits and subsequent psychotic illness (Reichenberg, 2005). Cognitive difficulties in early childhood can therefore be assumed to be important precursors of psychotic disorders in adulthood (Manzano et al., 1992; Jones et al., 1994). Interestingly, bivariate associations revealed no systematic relationships between psychotic illness (or other mental disorders) in family and IQ scores. Genetic liability plays a crucial role within the framework of cognition and mental illness (Jundong et al., 2011). Therefore, children of parents who suffer from schizophrenia are more likely than others to develop cognitive abnormalities during their life (Sobin et al., 2001; Hans et al., 2005). Our study, however, was not able to confirm such findings. A possible explanation might be that asking for familial disorders in our study was not explicitly restricted to the nuclear family so possibly considered

other family members that are genetically related. Though, our data supports an intergenerational (or at least within a genetic circle) association of psychopathology specifically a family history of a certain disorder increases the biological/genetic risk for the same disorder – independent of other influences (Stilo and Murray, 2010). Thus, psychotic disorders were most likely among offspring (or relatives) of a psychosis-affected family (Korkeila et al., 2011). The high congruence between self-reported familial psychopathology and clinical assessments supports the validity of our data since both kinds of information stem from independent sources.

Although positively associated in bivariate analysis an independent effect of birth complications on psychotic disorders was not confirmed by our data – probably due to the small number of subjects diagnosed with a psychosis. Within the framework of the neurodevelopmental hypothesis of schizophrenia (Murray & Lewis, 1987) obstetric factors (beside other adverse environmental influences) are assumed to aberrate a normal brain development and therefore to increase the risk for psychotic disorders (z.b. Moreno et al., 2009; Stilo and Murray, 2010). Also, a recent study found no direct effects of obstetric complications and developmental delays on the risk of developing schizophrenia whereas a cumulative effect of both factors was found to be significantly associated (Clarke et al., 2011). It is thought that obstetric factors might create a neural diathesis during brain development, which in turn may increase the risk for psychosis (Goldstein et al., 2000; Isohanni et al., 2004; Mrad et al., 2010). This aspect was, however, not explicitly tested in the current study. Although birth complications were positively related to mental disorders, bivariate analyses revealed positive associations between birth complications and VIQ or FSIQ. This finding was somewhat unexpected and might be explained by a lack of confounding factors in this bivariate association.

The present study has certain limitations due to the nature of our data, which need to be taken into account. First and most importantly, diagnoses of schizophrenia and related psychosis were all lumped together into a single category, which hampered to explore differential effects. Previous research suggests differences in cognitive functioning between schizophrenia, delusional disorders and schizoaffective disorders (Howard et al., 1994). Findings of a meta-analytic approach suggest that cognitive impairments are attributable to more severe negative symptoms in schizophrenia than in other diagnostic subgroups, although these differences were rather small (Bora et al., 2009). However, this leads to the third limitation of the current study insofar, that effects of several covariates, such as psychopathology, duration of untreated psychosis as well as antipsychotic drugs have not been controlled for. The literature suggests that both severity of positive and negative symptoms (Hughes et al., 2003) and longer durations of untreated psychoses (Amminger et al., 2002; Lappin et al., 2007) are linked to poorer cognitive performance in first episode psychosis. Effects of antipsychotic drugs on cognitive performance in patients with schizophrenia are not entirely clear: while some studies found positive effects (Selva-Vera et al., 2010; Shim et al., 2012) others found either no effects (Remillard et al., 2008; Kelly et al., 2009) or effects varying by type of medication (conventional/atypical) (Müller et al., 2005). Fourth, the individuals in our sample were all males. Despite the large numbers in our sample our data is restricted to a sample of young Swiss males therefore the findings cannot be directly extrapolated to other populations. Fifth, apart from diagnostic assessments and intelligence data all remaining information obtained for test purposes relied on self-reported data, which may lead to biased effects. It is generally difficult to obtain non-reactive or objective data with such an approach and in the context of military conscription where self-reports may be influenced by motivational factors this difficulty is significantly greater.

Specifically it may lead in some cases to overreporting of problems and in others to underreporting. One step taken in this study in order to minimize such effects was to allow individuals to leave answers blank. By the way, the authors are aware of the fact, that all "single item"-markers of pre existing cognitive problems and other covariates are recalled and therefore subject to a probable measurement error. However, for the sake of simplicity the use of more elaborated methods such as latent variable framework was abandoned. Finally, the IQ test selected for administration to the Swiss conscripts is not a well-established psychometric test, it has, however, been validated against internationally recognized measures (Huber, 1999). The data benefit from a large population base, which allowed the calculation of standard IQ scores. The division of intelligence into subdimensions of verbal and performance tasks revealed interesting trends. Although a more comprehensive cognitive assessment could help to explore further domain-specific differences such as memory (O'Connor et al., 2012) associations with type of impairment are controversial (Bechard-Evans et al., 2010).

Despite the limitations discussed in the previous section the present study provides strong evidence of a link between impaired intelligence and psychotic disorders, specifically impairments in performance (fluid) intelligence. Our findings suggest that cognitive impairments, assessed in first psychotic episode, may in many cases have their origins in early life. It supports the view of cognitive impairment as an early developmental process, which may increase the vulnerability for psychosis. According to the neurodevelopmental hypothesis of psychosis cognitive impairments are not isolated risk factors but rather work in combination with other factors (Owen et al., 2011). This may have important implications for the early detection of psychoses as well as for therapeutic approaches. First, it highlights the importance of cognitive assessments in addition to simply assessing clinical symptoms of psychotic experiences. Those who

show evidence of large cognitive deficits, especially in fluid (performance) functions, together with other identified risk factors, are likely to have a significantly higher risk of developing psychosis than those without such impairments (Harvey, 2009). Furthermore, it stresses the need for a broader therapeutic focus. Although it is important to aim on a reduction of psychotic symptoms, cognitive problems as well as negative symptoms should be additional targets in diagnosis and treatment of psychoses (Keefe and Fenton, 2007). Cognitive deficits may be a starting point for a personalized medicine in terms of placement, rehabilitation, medications and cognitive training.

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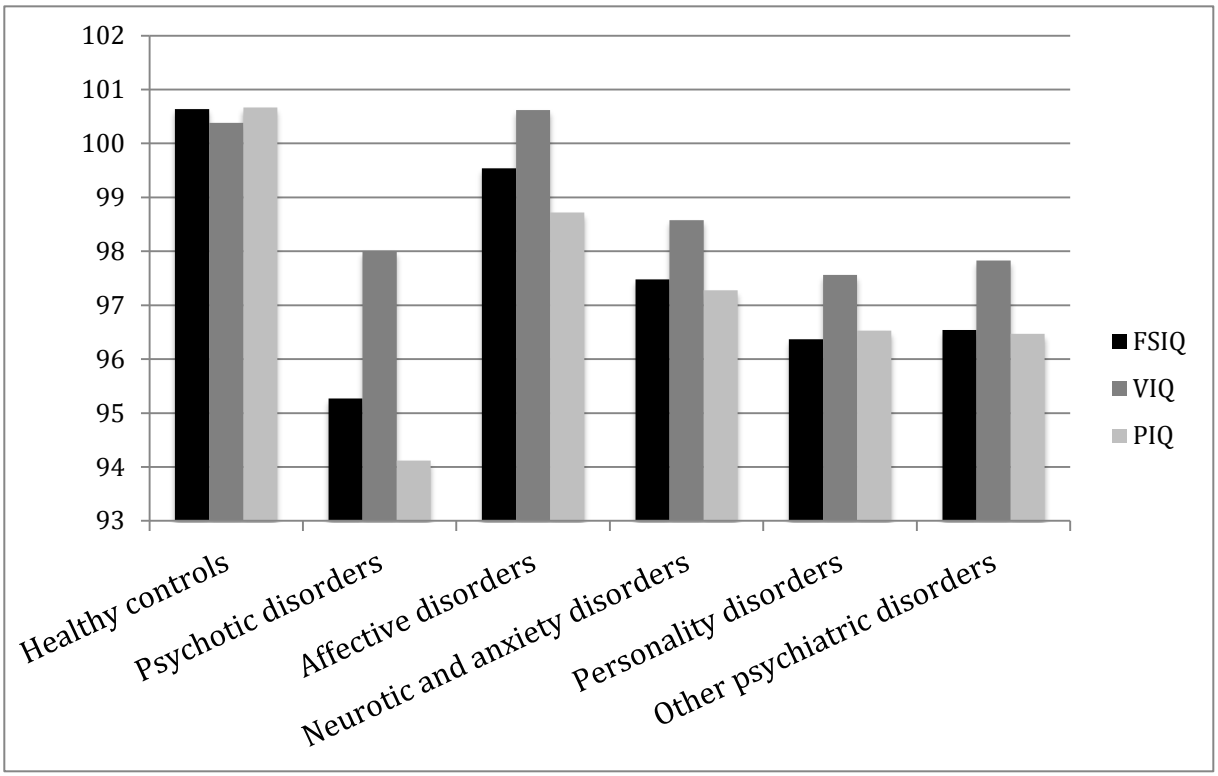

Fig 1.

Distributions of raw IQ scores across diagnostic categories

Tab 1.

Distributions of current IQ, markers of premorbid intellectual dysfunction and developmental factors across categories of psychiatric disorders

		Total sample (N=50,621; 100.00%)#	Study sample (N=49,545; 97.87%)							Study dropouts due to a possible prodrome (N=1,076; 2.13%)		
			Healthy controls (N=41,101; 82.96%)	Psychotic disorders (N=61; 0.12%)	Mood disorders (N=747; 1.51%)	Neurotic and anxiety disorders (N=2,916; N=5.89%)	Personality disorders (N=823; 1.66%)	Other psychiatric disorders (N=3,897; 7.87%)	p-value	Psychotic disorders (N=14; 0.03%)	Any other psychiatric disorder (N=1,062; 2.52%)	p-value
Current cognitive ability	FSIQ - M (SD)	100.00 (15.00)	100.64 (14.69)	95.27† (19.30)	99.54 (16.06)	97.48*** (16.55)	96.37*** (16.24)	96.54*** (15.64)	< 0.001	95.28 (14.34)	98.36*** (14.94)	< 0.001
	VIQ - M (SD)	100.00 (15.00)	100.38 (14.72)	98.00 (17.79)	100.62 (16.24)	98.58*** (16.70)	97.56*** (16.65)	97.83*** (15.54)	< 0.001	96.04 (14.77)	98.87** (15.13)	0.003
	PIQ - M (SD)	100.00 (15.00)	100.67 (14.83)	94.12** (18.44)	98.72** (15.14)	97.28*** (15.68)	96.53*** (14.92)	96.47*** (15.32)	< 0.001	95.79 (17.92)	98.46*** (14.98)	< 0.001
Markers of premorbid intellectual deficits	Not finished compulsory school (column %)	1.79	1.43	12.50	3.70	2.20	4.85	3.99	< 0.001	7.14	2.47	0.004
	Repeated class (column %)	23.50	22.03	55.17	34.41	26.81	38.50	31.00	< 0.001	50.00	22.78	0.035
	Under psychological review du to learning difficulties (column %)	10.13	7.79	29.82	22.95	19.51	23.04	23.43	< 0.001	21.43	7.22	n.s.
	Dyslexia (column %)	5.59	4.59	15.25	12.93	9.80	10.77	10.67	< 0.001	0.00	4.90	n.s.
Developmental factors	Schizophrenia or psychotic disorders in family (column %)	4.11	2.78	32.73	17.86	10.55	11.40	9.73	< 0.001	0.00	3.14	n.s.
	Depression in family (column %)	21.55	17.08	51.79	69.34	46.91	52.15	36.95	< 0.001	21.43	17.80	n.s.
	Anxiety disorders in family (column %)	8.76	6.42	16.67	31.84	24.41	27.68	14.98	< 0.001	7.14	6.60	n.s.

	Obsessive-compulsive disorders in family (column %)	2.34	1.50	9.43	11.56	6.83	8.90	5.14	< 0.001	7.14	1.91	n.s.
	Other disorders in family (column %)	36.33	31.26	68.97	71.62	60.92	64.05	59.31	< .001	21.43	34.15	n.s.
	Birth complications (column %)	12.77	11.11	23.21	24.61	21.25	21.65	20.77	< .001	0.00	10.55	n.s.

Note: IQ=intelligence quotient; FSIQ = full-scale IQ; VIQ = verbal IQ; PIQ = performance IQ;
p-values for mean difference tests in IQ scores according to ANOVA, Bonferroni post-hoc comparisons "against healthy controls" indicated by †p<.10 *p<.05 **p<.01 ***p<.001 ;
p-values for premorbid markers and other covariates according to Chi-Square statistics;
Total sample after exclusion of organic mental disorders, mental retardations and cases with missing IQ data

Tab 2.

Bivariate associations between markers of premorbid intellectual dysfunction and developmental factors with IQ

			FSIQ	p-value	VIQ	p-value	PIQ	p-value
School problems	Not finished compulsory school	No	100.31 (14.80)	< 0.001	100.28 (14.79)	< 0.001	100.24 (14.91)	< 0.001
		Yes	89.50 (17.69)		90.32 (18.33)		92.13 (15.39)	
	Repeated class	No	101.29 (14.69)	< 0.001	101.16 (14.67)	< 0.001	101.00 (14.89)	< 0.001
		Yes	96.23 (15.14)		96.63 (15.29)		97.09 (14.85)	
	Under psychological review due to learning difficulties	No	100.62 (14.77)	< 0.001	100.49 (14.78)	< 0.001	100.55 (14.88)	< 0.001
		Yes	95.53 (15.70)		96.57 (15.85)		96.02 (15.16)	
	Dyslexia	No	100.76 (14.65)	< 0.001	100.83 (14.61)	< 0.001	100.46 (14.86)	< 0.001
		Yes	89.09 (15.62)		87.77 (15.15)		93.75 (15.41)	
Developmental factors	Schizophrenia or psychotic disorders in family	No	100.10 (14.85)	0.016	100.03 (14.84)	< 0.001	100.14 (14.93)	n.s.
		Yes	100.93 (16.19)		101.98 (15.98)		99.71 (15.70)	
	Depression in family	No	99.60 (14.79)	< 0.001	99.32 (14.77)	< 0.001	99.98 (14.86)	0.003
		Yes	101.83 (15.18)		102.71 (15.03)		100.47 (15.27)	
	Anxiety disorders in family	No	100.04 (14.79)	0.008	99.88 (14.79)	< 0.001	100.16 (14.88)	0.002
		Yes	100.68 (15.94)		102.04 (15.84)		99.41 (15.61)	
	Obsessive-compulsive disorders in family	No	100.09 (14.86)	n.s.	100.04 (14.85)	0.049	100.10 (14.92)	n.s.
		Yes	100.13 (16.50)		100.92 (16.28)		99.44 (16.22)	
	Other disorders in family	No	100.07 (14.91)	n.s.	99.89 (14.92)	0.001	100.21 (14.92)	0.005
		Yes	100.08 (15.06)		100.35 (15.02)		99.82 (15.08)	
	Birth complications	No	99.99 (14.89)	< 0.001	99.83 (14.89)	< 0.001	100.13 (14.93)	n.s.
		Yes	100.83 (15.11)		101.63 (15.01)		99.86 (15.12)	

Note: p-values according to Chi-Square statistics; IQ=intelligence quotient; FSIQ = full-scale IQ; VIQ = verbal IQ; PIQ = performance IQ;

Tab 3.

Crude odds ratios for bivariate associations of intelligence test data, markers of premorbid intellectual dysfunction and developmental factors with diagnostic categories

	Psychotic disorders	Mood disorders	Neurotic and anxiety disorders	Personality disorders	Other psychiatric disorders
	OR (CI95%)	OR (CI95%)	OR (CI95%)	OR (CI95%)	OR (CI95%)
FSIQ (z-standardized)	0.70 (0.55-0.90)	n.s.	0.81 (0.78-0.84)	0.75 (0.70-0.81)	0.76 (0.74-0.79)
VIQ (z-standardized)	n.s.	n.s.	0.89 (0.86-0.92)	0.83 (0.78-0.89)	0.85 (0.82-0.87)
PIQ (z-standardized)	0.64 (0.50-0.83)	0.88 (0.82-0.94)	0.80 (0.77-0.83)	0.76 (0.71-0.81)	0.75 (0.73-0.78)
Not finished compulsory school	9.87 (4.45-21.88)	2.65 (1.79-3.93)	1.56 (1.20-2.02)	3.52 (2.53-4.91)	2.87 (2.40-3.44)
Repeated class	4.36 (2.60-7.31)	1.86 (1.59-2.16)	1.30 (1.19-1.41)	2.22 (1.92-2.56)	1.59 (1.48-1.71)
Under psychological review due to learning difficulties	5.03 (2.85-8.88)	3.53 (2.96-4.20)	2.87 (2.60-3.17)	3.54 (3.00-4.19)	3.62 (3.33-3.94)
Dyslexia	3.74 (1.84-7.62)	3.09 (2.47-3.85)	2.26 (1.98-2.58)	2.51 (2.00-3.15)	2.48 (2.22-2.78)
Schizophrenia or psychotic disorders in family	17.02 (9.66-30.00)	7.61 (6.20-9.34)	4.13 (3.60-4.73)	4.50 (3.58-5.67)	3.77 (3.33-4.27)
Depression in family	5.21 (3.09-8.81)	10.98 (9.33-12.92)	4.29 (3.96-4.65)	5.29 (4.58-6.11)	2.85 (2.65-3.06)
Anxiety disorders in family	2.92 (1.42-5.97)	6.81 (5.77-8.03)	4.71 (4.28-5.18)	5.58 (4.74-6.57)	2.57 (2.33-2.83)
Obsessive-compulsive disorders in family	6.86 (2.72-17.29)	8.60 (6.70-11.04)	4.83 (4.08-5.72)	6.43 (4.96-8.34)	3.56 (3.02-4.21)
Other disorders in family	4.89 (2.80-8.53)	5.55 (4.72-6.52)	3.43 (3.17-3.70)	3.92 (3.39-4.53)	3.21 (3.00-3.43)
Birth complications	2.42 (1.30-4.50)	2.61 (2.20-3.11)	2.16 (1.96-2.38)	2.21 (1.86-2.62)	2.10 (1.93-2.28)

Note: IQ=intelligence quotient; FSIQ = full-scale IQ; VIQ = verbal IQ; PIQ = performance IQ; OR=odds ratio; CI95%= 95% confidence interval

Tab 4.

Adjusted multinomial logistic regression models: Full and subscale IQ, markers of premorbid intellectual dysfunction and developmental factors as predictors of diagnostic categories

		Psychotic disorders	Mood disorders	Neurotic and anxiety disorders	Personality disorders	Other psychiatric disorders
		OR (CI95%)	**OR (CI95%)**	**OR (CI95%)**	**OR (CI95%)**	**OR (CI95%)**
	FSIQ (z-standardized)	**0.66 (0.50-0.89)**	**0.88 (0.81-0.96)**	**0.79 (0.76-0.83)**	**0.78 (0.72-0.85)**	**0.78 (0.75-0.81)**
	VIQ (z-standardized)	n.s.	n.s.	0.89 (0.85-0.93)	0.91 (0.84-0.99)	0.92 (0.88-0.95)
	PIQ (z-standardized)	0.64 (0.47-0.88)	0.88 (0.81-0.97)	0.85 (0.81-0.89)	0.82 (0.76-0.89)	0.81 (0.78-0.84)
School problems	Not finished compulsory school	**3.05 (1.13-8.26)** 3.10 (1.14-8.37)	**n.s.** n.s.	**n.s.** n.s.	**1.89 (1.29-2.79)** 1.91 (1.29-2.81)	**1.67 (1.35-2.06)** 1.68 (1.36-2.07)
	Repeated class	**2.37 (1.31-4.30)** 2.39 (1.32-4.34)	**n.s.** n.s.	**n.s.** n.s.	**1.47 (1.25-1.74)** 1.48 (1.25-1.75)	**n.s.** n.s.
	Under psychological review due to learning difficulties	**2.36 (1.21-4.59)** 2.34 (1.20-4.55)	**1.81 (1.47-2.24)** 1.80 (1.46-2.23)	**1.81 (1.61-2.04)** 1.81 (1.61-2.04)	**1.81 (1.48-2.21)** 1.80 (1.47-2.21)	**2.37 (2.16-2.61)** 2.36 (2.15-2.60)
	Dyslexia	**n.s.** n.s.	**1.74 (1.33-2.28)** 1.78 (1.36-2.34)	**1.33 (1.13-1.55)** 1.34 (1.14-1.56)	**n.s.** n.s.	**1.24 (1.09-1.42)** 1.27 (1.11-1.46)
Developmental factors	Schizophrenia or psychotic disorders in family	**5.76 (2.71-12.23)** 5.75 (2.71-12.21)	**1.69 (1.33-2.16)** 1.69 (1.32-2.16)	**1.37 (1.16-1.61)** 1.36 (1.16-1.60)	**n.s.** n.s.	**1.57 (1.36-1.82)** 1.57 (1.36-1.82)
	Depression in family	**2.02 (1.02-3.99)** n.s.	**5.44 (4.48-6.62)** 5.40 (4.44-6.57)	**2.26 (2.05-2.50)** 2.26 (2.05-2.49)	**2.58 (2.16-3.08)** 2.56 (2.14-3.06)	**1.66 (1.52-1.82)** 1.65 (1.51-1.80)
	Anxiety disorders in family	**n.s.** n.s.	**1.77 (1.44-2.17)** 1.76 (1.44-2.16)	**2.08 (1.85-2.34)** 2.08 (1.85-2.34)	**2.07 (1.69-2.53)** 2.06 (1.68-2.53)	**1.24 (1.10-1.40)** 1.23 (1.09-1.39)
	Obsessive-compulsive disorders in family	**n.s.** n.s.	**1.88 (1.39-2.52)** 1.88 (1.40-2.53)	**1.55 (1.27-1.90)** 1.55 (1.27-1.90)	**1.80 (1.32-2.46)** 1.80 (1.32-2.46)	**1.42 (1.16-1.73)** 1.42 (1.16-1.73)
	Other disorders in family	**2.08 (1.07-4.03)** 2.09 (1.08-4.05)	**2.21 (1.82-2.68)** 2.21 (1.82-2.68)	**2.11 (1.92-2.31)** 2.11 (1.92-2.32)	**2.41 (2.02-2.87)** 2.41 (2.02-2.88)	**2.29 (2.12-2.48)** 2.29 (2.12-2.48)
	Birth complications	**n.s.** n.s.	**1.54 (1.27-1.88)** 1.54 (1.27-1.88)	**1.52 (1.36-1.69)** 1.52 (1.36-1.69)	**1.53 (1.27-1.86)** 1.53 (1.26-1.85)	**1.56 (1.42-1.72)** 1.56 (1.42-1.71)

Note: IQ=intelligence quotient; FSIQ = full-scale IQ; VIQ = verbal IQ; PIQ = performance IQ; OR=odds ratio; CI95%= 95% confidence interval; full scale IQ (printed in bold) and subscale IQ were analyzed in separate models